Journal of Advanced Scientific Research

Available online through https://sciensage.info

ISSN

0976-9595

Research Article

Formulation and Evaluation of Polyherbal Antidiabetic Capsules

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Received: 28-02-2024; Accepted: 15-03-2024; Published: 30-03-2024

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https://doi.org/10.55218/JASR.2024150305

ABSTRACT

This research aims to create and assess polyherbal antidiabetic capsules using medicinal plants with antidiabetic properties. The formulation process involves carefully choosing botanical extracts with antidiabetic properties, verifying their bioactive compounds, and blending them to form a polyherbal blend with maximum antidiabetic potential while ensuring safety. Microcrystalline cellulose is used in encapsulating a polyherbal mix for stability, release, and patient convenience. A capsule dosage form is recommended for improved treatment adherence. Efficiency is assessed through *in vitro* studies on enzymes involved in glucose metabolism and their inhibitory effect. The results of this study offer a viable natural option for managing diabetes by providing important insights into the composition of polyherbal antidiabetic capsules. Several botanical extracts with complimentary modes of action have the potential to be combined, offering a comprehensive strategy to address the complex nature of diabetes mellitus. Nevertheless, more clinical studies, including diabetes patients, are necessary to confirm the capsules' long-term advantages, safety, and effectiveness. The formulation of polyherbal antidiabetic capsules may present novel approaches to the management of diabetes, enhancing glycaemic control and elevating the standard of living for those with the condition.

Keywords: Diabetes mellitus, Hyperglycemia, Botanical extracts, Polyherbal capsules.

INTRODUCTION

Traditional medicine, also known as folk medicine, was made up of knowledge systems that were developed over many centuries across many civilizations prior to the development of modern medicine.

Traditional medicine, as defined by the World Health Organisation (WHO), is the sum of all knowledge, skills, and practices that originate from indigenous beliefs, experiences, and notions from different cultures, regardless of their explanation. It's used to prevent, diagnose, treat, or improve physical and mental health issues in addition to maintaining good health.

In several Asian and African countries, up to 80% of the population use traditional medicine for their fundamental medical requirements. Traditional medicine is occasionally referred to as complementary or alternative medicine when used outside of its own culture.[1,2]

Elevated blood sugar levels are a hallmark of diabetes, a metabolic condition caused by inadequate insulin synthesis by the pancreatic gland or insufficient cell responsiveness to insulin. The body uses glucose as its main energy source when food is digested properly. Insulin is created and released by the pancreas to transport glucose into the cells. Usually, the pancreas produces insulin naturally based on the quantity of glucose present. However, in people with diabetes, the pancreas either doesn't produce any insulin at all or produces so little that the cells become resistant to it.[3-6]

Types of Diabetes[7]

Type-1 Diabetes mellitus

Type 1 diabetes (formerly known as insulin-dependent) is when the pancreas fails to produce the insulin essential for survival. This form develops most frequently in children and adolescents.

Type-2 Diabetes mellitus

Type 2 diabetes (formerly named non-insulin-dependent) results from the body's inability to respond properly to the action of insulin produced by the pancreas. Type 2 diabetes is much more common and accounts for around 90% of all diabetes cases worldwide. It occurs most frequently in adults but is also noted increasingly in adolescents.

Gestational Diabetes

Diabetes that's triggered by pregnancy is called gestational diabetes (pregnancy, to some degree, leads to insulin resistance). It is often diagnosed in the middle or late pregnancy. Because high blood sugar levels in a mother are circulated through the placenta to the baby,

gestational diabetes must be controlled to protect the baby's growth and development. The rate of gestational diabetes is between 2 to 10% of pregnancies.

Management of diabetes mellitus through natural herbs

Patients seeking to use natural antidiabetic treatments are becoming more and more common as a result of side effects from the administration of insulin and oral hypoglycemic medications. With the growing interest in botanical remedies and alternative medicine, biologists, chemical researchers, pharmacologists and biochemists have banded together to search for natural substances that might prevent or mitigate diabetes mellitus and its related complications.

Herbs and herbal formulations used commonly in the management of diabetes mellitus are *Tinospora cordifolia* or guduchi, *Linum usitatissimum* or flax seeds, *Murraya koenigii* or curry leaves *and Trigonella foenumgraecum* or Methi.(8,9)

It is challenging to find an antidiabetic drug that works either on its own or in combination. A decoction of the mixture was advised in terms of ethnomedicine. Studies that have been published indicate that the decoction has a shelf life of only three hours, during which it can become unstable due to changes in temperature, pressure, or microbes. The traditional dosage type has a harsh flavour as well. Our plan was to circumvent these problems by developing an extract of ethanol and using it as a suitable vehicle for medication delivery in the form of capsules. It was intended to guarantee that the capsules would fulfil the pharmacopeial quality requirements and exhibit an active component release similar to a conventional dosage form.

Thus we have planned to develop an antidiabetic herbal formulation using ethanolic extracts of *T. foenum graecum* (seeds), *L. usitatissimum seeds* (seeds), *M. koenigii* (leaves), *T. cordifolia* (leaves).

EXPERIMENTAL AND RESULTS

The designed polyherbal antidiabetic formulation consists of four types of herbs including *T. foenum graecum* (seeds), *L. usitatissimum seeds* (seeds), *M. koenigii* (leaves), and *T. cordifolia* (leaves).

Since all of the chosen plants were found within or near the area, they were personally picked up from their designated locations in May through July of 2023.

The plant components that were acquired were meticulously cleansed. After that, they were dried for about a week in the shade. After they been dried fully, crushed into a coarse powder (as shown in Fig 1), kept in airtight receptacles and kept ready for additional processing.

Extraction of Crude Drugs

Extraction of T. foenum graecum:

The fresh *T. foenum-graecum* seeds were allowed to air dry before being processed using a grinding machine into a powder. The powder of 1.5 kg was extracted in Erlenmeyer flasks at room temperature using 90% ethanol. The maceration process involved five times every 48 hours, interspersed with irregular stirring and shaking. 150 gm of crude extract were obtained by mixing the entire extract, filtering it using Whatman filter paper No. 1, condensing it under vacuum at 40°C, and freezing it until it was completely dry.

Fig. 1: Powdered form of herbal crude drugs

Extraction of T. cordifolia:

Tiny pieces of *T. cordifolia* leaves were cut and baked at 40°C to dry them out. It was then ground and stored at 4°C for subsequent use. The following solvents were used in a serial way to extract the stem powder of *T. cordifolia*: water, methanol, ethanol, acetone, ethyl acetate, and chloroform-ether (1:1), in that order. The findings were combined after extracting twice (each with 500 mL solvent). Each individual extract's solvents were flash vaporized to dryness, lyophilized, and then reconstituted with water.

Extraction of M. koenigii:

The maceration method was used to create an aqueous extract of *M. koenigii* leaves. About 200 g of powdered leaves were macerated cold using chloroform: water ratio in a conical flask that was stored at room temperature for seven days. The lip of the flask was sealed with moist cotton, and it was shaken often. After passing it through a muslin cloth, the filtrate was further filtered using Whatman filter paper to provide a clear filtrate. The leftover residue was dried and concentrated by shade-drying the filtrate for 30 days.

Extraction of L. usitatissimum:

L. usitatissimum seeds were properly cleaned using filtered water. The seeds were mashed and dried to form powder. About 50 gm of dried seeds powder was extracted using a soxhlet apparatus. A week-long population at 30°C was done to obtain the extract. For phytochemical analysis, crude was produced by evaporating the extracted material at 70°C in a water bath. The extraction was maintained at 40°C in an airtight container. An incubator was set up for a week at 25°C with five vibrations per day minimum after the cold extraction of 50 gm of dry powder with 200 mL of petroleum ether using a rotary shaker. This extract was kept in storage at 40°C following a 24-hour drying cycle at 500°C.

Phytochemical Analysis of Herbal Extracts

After the completion of crude drug extraction, obtained extracts were subjected to phytochemical analysis to determine the presence of essential phytochemical constituents in them and the results obtained were mentioned in Table 1.

Evaluation of Organoleptic Characteristics

This study evaluated organoleptic characteristics like the collected and powdered herbs' appearance, taste, and odor. The observations are mentioned in the Table 2.

Evaluation of Physicochemical Properties

Loss on drying

Ten gm of the medication was measured in a tarred flat weighing vial that had been previously dried for five hours at 105°C, chilled in

Table 1: Presence of phytochemical constituents in herbal extracts

S. No	Herbal extract	Tannins	Alkaloids	Flavonoids	Terpenoids	Saponins
1	T. foenum graecum	+	+	+	+	+
2	*L. usitatissimum*	+	+	+	+	+
3	*T. cordifolia*	+	+	+	-	+
4	*M. koenigii*	+	+	+	-	+

Table 2: Organoleptic characters

S.No	Name of the plant	Nature	Color	Odor	Taste
1	*T. foenumgraecum*	Coarse powder	Pale yellowish	Pungent	Bitter
2	*M. koenigii*	Coarse powder	Dark greenish	Pleasant	Astringent
3	*L. usitatissimum*	Coarse powder	Grey to light brown	Odorless	Sore to light bitter
4	*T. cordifolia*	Coarse powder	Dull greenish	Pungent	Pleasant

an appropriate desiccator, and then weighed. Every hour, the drying process was continued and the weight was maintained at a steady level as mentioned in Table 3.

$$\text{Loss on drying \%} = \frac{\text{Final weight of the sample}}{\text{Initial weight of the sample}} \times 100$$

Total ash value

2 gm of the powdered medication were burned at 450 degrees Celsius in a muffle furnace until the carbon burned entirely and the weight of the crucible remained constant. The crucible was then taken out, allowed to cool in an appropriate desiccator for half an hour, and then the contents were weighed. Using the medicine that had been air-dried as a reference, the percentage of total ash content was determined and noted down in Table 4.

$$\text{\% Total ash} = \frac{\text{Weight of residue obtained}}{\text{Weight of sample taken}} \times 100$$

Acid insoluble ash value

25 ml of diluted hydrochloric acid was used to boil the complete amount of ash for five minutes. The insoluble material was then collected in ashless filter paper, cleaned with hot water, and burned at 4500C to maintain weight. The air-dried medication was used as a reference to compute the percentage of acid insoluble ash content. The values obtained were mentioned in Table 5.

$$\text{\% Acid insoluble ash} = \frac{\text{Weight of residue obtained}}{\text{Weight of sample taken}} \times 100$$

Water soluble ash value

25 ml of water was added into the crucible containing all of the ash, then boiled for 5 min. The insoluble material was gathered onto ashless filter paper. After washing in hot water, the retained material was placed in a crucible and heated it for 15 minutes, not going beyond 450°C. Deduction of this residue's weight in milligrams (mg) from

Table 3: Loss on drying

S. No	Plant name	LOD (% w/w)	Acceptable limits (w/w %)
1	*T. foenum-graecum*	2.74 ± 0.59	NMT 8
2	*M. koenigii*	3.67 ± 0.12	NMT 8
3	*L. usitatissimum*	3.67 ± 0.12	NMT 6
4	*T. cordifolia*	4.16 ± 0.07	NMT 5

The value are expressed as mean ± SD, (n = 3); NMT-Not more than

Table 4: Total ash value

S. No	Plant name	Total ash (% w/w)	Acceptable limits (w/w %)
1	*T. foenum-graecum*	4.064 ± 0.12	NMT 14
2	*M. koenigii*	2.31 ± 0.02	NMT 5
3	*L. usitatissimum*	5.36 ± 2.23	NMT 7
4	*T. cordifolia*	5.16 ± 0.04	NMT 7

The value are expressed as mean ± SD, (n = 3); NMT-Not more than

Table 5: Acid insoluble ash value

S. No	Plant name	Acid insoluble ash (% w/w)	Acceptable limits (w/w %)
1	*T. foenum-graecum*	0.34 ± 0.08	NMT5
2	*M. koenigii*	0.45 ± 0.02	NMT5
3	*L. usitatissimum*	1.17 ± 0.16	NMT2
4	*T. cordifolia*	0.68 ± 0.01	NMT1

The value are expressed as mean ± SD, (n = 3); NMT-Not more than

Table 6: Water soluble ash value

S.No	Plant name	Water soluble ash (% w/w)	Acceptable limits (w/w %)
1	*T. foenum-graecum*	0.78 ± 0.01	NMT 3
2	*M. koenigii*	2.31 ± 0.02	NMT 5
3	*L. usitatissimum*	1.76 ± 0.37	NMT 3
4	*T. cordifolia*	2.74 ± 0.59	NMT 6

The value are expressed as mean ± SD, (n = 3); NMT-Not more than

Table 7: UV absorbance values of polyherbal extract

S. No	*Concentration (µg/ml)*	*Absorbance (nm)*
1	0	0.060 ± 0.1
2	2	0.142 ± 0.15
3	4	0.261 ± 0.19
4	6	0.383 ± 0.2
5	8	0.501 ± 0.26
6	10	0.644 ± 0.3

Each value of absorbance indicated with S.D (n = 3)

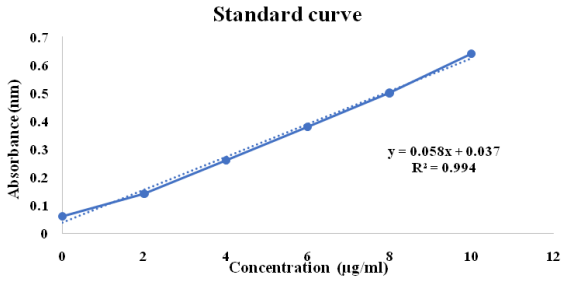

Fig. 2: Calibration curve of polyherbal extract in pH 1.5 buffer

the overall ash weight gives water insoluble ash value per gm of air-dried material as shown in Table 6.

$$\% \text{ Water soluble ash} = \frac{\text{Weight of residue obtained}}{\text{Weight of sample taken}} \times 100$$

Calibration of polyherbal extract in 0.1N HCl buffer

By diluting the polyherbal extract in pH 1.5 HCl buffer, a workable stock of 1000 µg/mL was created. A UV-visible spectrophotometer was used to measure absorbance after primary and secondary dilutions were made. Beer's law compliance was confirmed across a 2 to 10 µg/mL range by recording the values in Table 7 and plotting a linear graph of absorbance vs. concentration as shown in Fig 2.

Table 8: Development of formulation

S. No	*Materials*	*Trial-1 (mg)*	*Trial-2 (mg)*	*Trial-3 (mg)*
1	*T. foenum-graecum*	40	30	60
2	*M. koenigii*	30	40	40
3	*L. usitatissimum*	30	50	33
4	*T. cordifolia*	50	30	50
5	Lactose	55	50	40
6	Micro crystalline cellulose	40	45	23
7	Magnesium carbonate	4.5	4.5	3.5
8	Sodium methylparaben	0.5	0.5	0.5
9	Starch paste	Aq	Aq	Aq

Table 9: Evaluation of flow properties

Parameters	*Trial 1*	*Trial 2*	*Trial 3*
Bulk density (g/mL)	0.78 ± 0.04	0.80 ± 0.05	0.90 ± 0.04
Tapped density (g/mL)	1.04 ± 0.02	1.02 ± 0.03	1.01 ± 0.04
Compressibility index (% w/w)	29 ± 0.03	23.5 ± 0.63	11.8 ± 0.04
Hausner's Ratio	1.35 ± 0.02	1.27 ± 0.02	1.12 ± 0.12
Angle of repose (degrees)	48.05 ± 1.0	39.66 ± 0.02	33.03 ± 3.78

The value are expressed as mean ± SD, (n = 3); NMT-Not more than

Development of polyherbal formulation

The following extracts underwent the freeze-drying process: T. foenum graecum (seeds), M. koenigii (dried leaves), L. usitatissimum (seeds), and T. cordifolia (dried leaves). The drying charge of the extracts dictated how long they took to dry. Following protocol-compliant weighing of each active ingredient, a thorough mixing process was performed with magnesium stearate (used as a lubricant), MCC, and diluents. Mixing the aggregate well took thirty minutes. The material was placed in the polythene luggage after being marked for additional research. Three trial batches of capsules were made (as shown in Fig 3) with various excipient compositions (as mentioned in Table 8) in order to produce better waft belongings. The bulk density, tapped density, compressibility index, Hausner's ratio, and angle of repose of the combined powder from all three experimental batches were examined and the results were noted down in Table 9.

Preformulation studies

Bulk density (ρb)

It is decided by measuring the extent of a regarded mass of powder pattern passed via a screen into a graduated cylinder or via a measuring apparatus into a cup. It is expressed in g/ml and is given through,

$$\rho b = M/Vo$$

Where, M - is the mass of powder

Vo- is the majority extent of the powder.

Tapped density (ρt)

The weighted amount of powder is transferred to a measuring cylinder and mechanically tapped to ascertain the volume of 200 tapping's, which is known as the tapped volume, in order to produce a measured volume V. It is expressed in g/mL and is given

Fig. 3: Formulated polyherbal anti-diabetic capsules

Table 10: Evaluation of physical parameters

S. No	Parameter	Observation		
		F1	F2	F3
1	Description	Light green colored granules filled in dull white cap and body "3" size capsule	Light green colored granules filled in dull white cap and body "3" size capsule	Light green colored granules filled in dull white cap and body "3" size capsule
2	Color	Light green granules	Light green granules	Light green granules
3	Odor	Characteristic odor	Characteristic odor	Characteristic odor
4	Taste	Bitter taste	Bitter taste	Bitter taste
5	pH (1% aqueous solution)	7.33 ± 0.21	7.5 ± 0.3	7.4 ± 0.41
6	Moisture content (%w/w)	13.72 ± 0.8	13.78 ± 0.9	13.5 ± 0.5
7	Uniformity of weight (mg)	92 ± 3.4	90 ± 3.6	98 ± 3.2
8	Disintegration time (min)	6'20 ± 0.34	8'30 ± 0.4	10'45 ± 0.46

Results are reported as Mean ± Standard deviation

$$\rho t = M/Vt$$

Where, M - Mass of powder

Vt- Tapped volume of the powder

Compressibility index

It is an oblique method of measuring the powder flow. It was given the Carr's index name since it was developed by a scientist named Carr. It is defined as the accurate assessment of the potential strength and stability of a bridge, arch, or structure. The percentage compressibility index (CI) is calculated by using formula.

$$CI = Vo\text{-}Vi \times 100/Vo$$

Where, Vo- Untapped density; Vi- Tapped density

Hausner's ratio

The granular material's frictional resistance is being measured. Based on the ratio of tapped density to bulk density, the ideal range is between 1.2 and 1.5.

$$\text{Hausner's ratio} = Vi / Vo$$

Where, Vo -Untapped density, Vi -Tapped density

Angle of repose

This angle of repose's tangent equals the particles' coefficient of friction. Consequently, the angle of repose will increase with the rougher and more irregular particle surface. In order to calculate the angle of repose (θ), the mixtures were placed into a funnel and its bottom tip was positioned precisely 2.0 cm above a hard surface. The medicine or mixes were added until the top tip of the pile surface contacted the bottom tip of the funnel. Angle of repose was calculated using the following equation.

$$\text{Tan } \theta = h/r,$$

$$\theta = \tan\text{-}1\ (h/r)$$

Where, θ - angle of repose,

h - height in cm and r- radius in cm.

Table 11: *In-vitro* dissolution studies of formulated polyherbal capsules

Time interval (min)	%Cumulative drug release		
	F1	F2	F3
0	0	0	0
10	6 ± 0.02	8 ± 0.03	12 ± 0.06
20	14 ± 0.12	20 ± 0.51	30 ± 0.31
30	30 ± 0.35	43 ± 0.25	55 ± 0.25
40	52 ± 0.2	64 ± 0.34	80 ± 0.42
50	70 ± 0.21	81 ± 0.16	92 ± 0.35
60	75 ± 0.36	87 ± 0.52	96 ± 0.26
70	80 ± 0.57	90 ± 0.64	98.9 ± 0.45

Each value of absorbance indicated with S.D (n = 3)

Formulation of polyherbal capsules using the wet granulation method

It is necessary to calculate how much material will fit within the capsule. Sizes ranging from "0" to "4" were commonly accessible in the market, and throughout the development phase, the correlation between the capsule size and associated body volume was established. Because ingesting bigger size capsules can be challenging, it is uncommon to utilize a size larger than a "0" for pharmaceutical items. Similarly, size "5" is rarely used because of issues with the automatic filling process. Size "3" capsules were chosen to be used in the polyherbal formulation.

The powder mix grains were created using the wet granulation process, which uses MCC as a polymer and starch as a granulating agent. To create granules, the wet material was run through sieve number 12, and they were then dried at 60°C in a hot air oven. The final product, granules, were manually put into "3" size capsules until the average net content weight of each capsule was around 250 mg.

Following dedusting, the capsules were placed into polythene bags tagged, and the samples were assessed in accordance with the testing specifications.

Standardization of the finished capsules

The produced polyherbal capsules were evaluated based on their description, weight homogeneity, disintegration time, moisture content, pH, and dissolving profile. The weight homogeneity was assessed using Indian Pharmacopeial standards. The values obtained were mentioned in Table 10.

Table 12: Order of drug release kinetics for optimized formulation (F3)

Zero-order		*First-order*		*Higuchi*		*Peppas*	
Time	*%CDR*	*Time*	*Log % cumulative drug remaining*	*SQRT Time*	*%CDR*	*Log time*	*Log %CDR*
0	0	0	2	0	0	0	0
10	12	10	1.944483	3.16228	12	1	1.079181
20	30	20	1.845098	4.47214	30	1.30103	1.477121
30	55	30	1.653213	5.47723	55	1.47712	1.740363
40	80	40	1.30103	6.32456	80	1.60206	1.90309
50	92	50	0.90309	7.07107	92	1.69897	1.963788
60	96	60	0.60206	7.74597	96	1.77815	1.982271
70	98.9	70	0.041393	8.3666	98.9	1.8451	1.995196

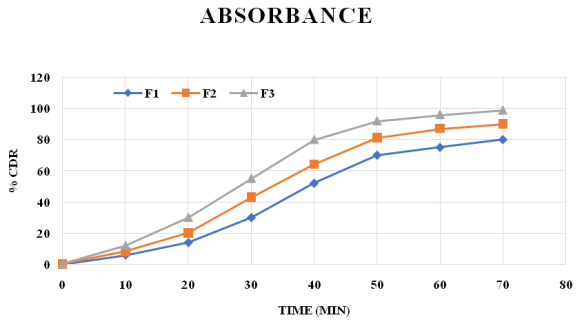

Fig. 4: *In-vitro* dissolution studies of formulated polyherbal capsules

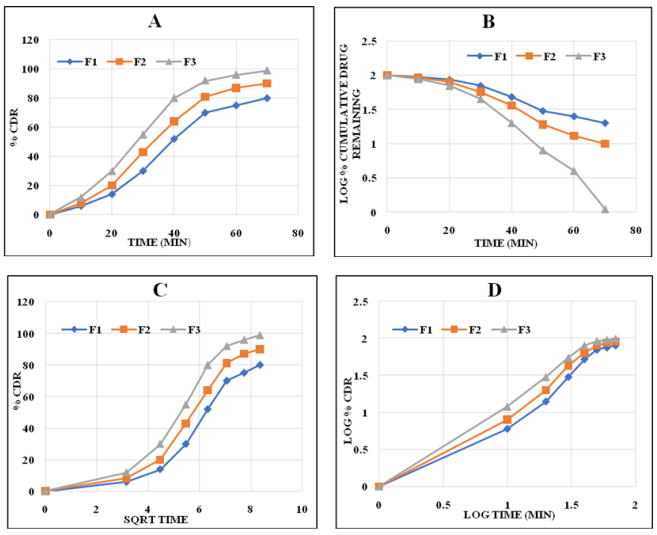

Fig 5: Drug release kinetics indicating (A) Zero order (B) First order (C) Higuchi model and (D) korsemeyer-Peppas model

In-vitro Dissolution Study

In-vitro dissolution studies for polyherbal antidiabetic capsules were carried out using USP apparatus type I at 50 rpm. The dissolution medium used was pH 1.5 HCL buffer (900 mL) maintained at 37 ± 0.5oC.

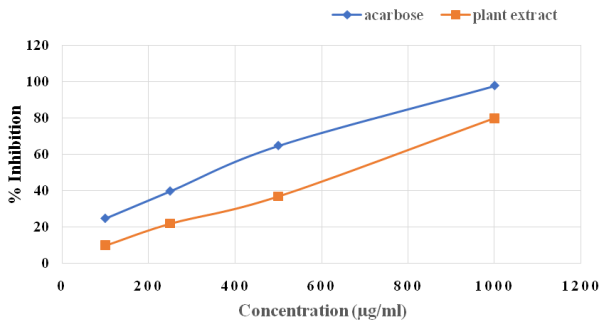

Fig. 6: α-Amylase inhibition assay

Table 13: α-amylase inhibition assay

Compound	*Concentration (µg/mL)*	*Absorbance (nm)*	*%inhibition*
Acarbose	100	0.209	25
	250	0.226	40
	500	0.284	65
	1000	0.339	98
Polyherbal extract	100	0.256	10
	250	0.344	22
	500	0.528	37
	1000	0.816	90

Samples (5 mL each) were withdrawn from the dissolution media for every 10 minutes of time interval. Absorbance was measured at 210 nm for the samples using a UV-visible spectrophotometer and cumulative drug release (%CDR) was determined simultaneously until maximum drug release was obtained. The results obtained were mentioned in Table 11 and graph was plotted as shown in Fig. 4.

Order of kinetics for *in-vitro* drug release studies

Based on the in-vitro drug release studies of polyherbal antidiabetic capsules, kinetics studies were performed for the optimized formulation. The results obtained were recorded as shown in Table 12 and graphs were plotted accordingly as shown in Fig 5.

Pharmacological evaluation

α-amylase inhibition assay

α-amylase was dissolved at a 0.1 mg/mL concentration in phosphate buffer saline (PBS, 0.02 mol/L, pH 6.8). For five minutes, α-amylase solution (0.010 mL) was combined with various concentrations of solutions for samples (0.25 mL) and incubated at 37°C. Then, 0.1 ml of a 1.0% (w/v) starch substrate solution was added to the incubation medium to start the reaction. The reaction was halted by adding 1-mL of DNS reagent (1% Dinitro salicylic acid, 0.05% Na2SO3, and 1% NaOH solution) to the reaction mixture and boiling it for 5 minutes at 100°C after it had been incubated for 3 minutes at 37°C. A spectrophotometer was used to measure the absorbance (Abs) at 540 nm after the sample had cooled to room temperature. The results obtained were mentioned in Table 13 and graph was plotted as shown in Fig. 6.

The following equation calculated the inhibition percentage:

$$\% \text{ inhibition} = \frac{\text{Absorbance control} - \text{Absorbance standard}}{\text{Absorbance control}} \times 100$$

CONCLUSION

Herbal remedies have been used to diagnose, prevent, and treat various illnesses. Four herbal raw materials were chosen for their potential to treat diabetes, including antioxidants, terpenoids, steroids, flavonoids, and alkaloids. The mixtures were combined into polyherbal capsules and tested for antidiabetic efficacy. The Ayurvedic Pharmacopoeia of India and WHO's recommended criteria were used to ensure quality. Three distinct trial batches were created, and the F3 formulation was found to be the most optimal, with a maximum drug release of 98.9% at 70 minutes.

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HOW TO CITE THIS ARTICLE: Geetha K, Bhavani V, Kiran RS, Rao TR. Formulation and Evaluation of Polyherbal Antidiabetic Capsules. *J Adv Sci Res*. 2024;15(3): 22-28 **DOI:** 10.55218/JASR.2024150305